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| 10/091,061 | 03/05/2002 | Francis Y.F. Lee | LD0268 NP | 6706 |

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| EXAMINER | |
|---|---|
| JIANG, SHAOJIA A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/091,061 | LEE, FRANCIS Y.F. | |
| | Examiner | Art Unit | |
| | Shaojia A. Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *101-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

In view of the appeal brief filed on July 21, 2004, PROSECUTION IS HEREBY REOPENED. Therefore, Applicant's amendment and response filed January 15, 2003 will be entered herein, wherein all previous claims 1-100 are cancelled; claims 101-112 are newly submitted.

Therefore, all rejections of record in the previous Office Action February 26, 2004 are withdrawn. The following is the new ground(s) of rejection(s).

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Applicant's claim for domestic priority to provisional applications Serial No. 60275801 and 60316395 under 35 U.S.C. 119(e) is acknowledged.

New Claims 101-112 are examined on the merits herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 101-112 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for treating specific cancers or tumors in the specification, does not reasonably provide enablement for **any cancers** broadly encompassed by the claims herein by administering the VERY same combination herein. Note that the recitation "cancer" may broadly encompass all known and **unknown** cancers as of the instant filing date.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention: The instant invention pertains to a method of treating cancer broadly comprising administering the instant combination.

2. The state of the prior art: The skilled artisan would view tumors as a group of maladies (cancers) not treatable with one medicament or therapeutic regimen.

Treatment efforts and efforts to cure all tumors (cancers) have produced only isolated identifiable positive results. See *In re Application of Hozumi et al.*, 226 USPQ 353.

3. The predictability of the art, and the breadth of the claims: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Moreover, it is known that repeated therapeutic failures, after promising in-vitro test results, suggest to the skilled artisan that claims based on in-vitro data, directed to treating cancer generally, are highly unpredictable, as taught in Trisha Gura's article in *Science*, November, 1997, Vol. 278, page 1041-1042 (PTO-892): "[T]he institute started by pulling together mouse models of three tumors: a leukemia, which affects blood cells; a sarcoma, which arise in bone, muscle, or connective tissue; and carcinoma, the most common cells and includes such major killers as breast, colon, and lung cancers. Initially, many of the agents tested in these models appeared to do well. However, most worked against blood cancers such as leukemia and lymphoma, as opposed to the more common solid tumors. And when tested in human cancer patients, most of these compounds failed to live up to their early promise." (emphasis added, see for example, the middle column of the article).

Based on the known teachings of the cancer treatment such as in Trisha Gura's reference, one of skill in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors which encompass, for examples, gynacological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer,

adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CNS, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by administering the very same combination.

4. The presence of absence of working examples:

Note that the specification provides no working example, i.e., testing the instant combination for treating a cancer (see the combination testing at Example at page 68-70). Moreover, the evidence in the examples herein is **not** commensurate in **scope** with the claimed invention and does not demonstrate criticality of numerous and various cancers or tumors in the claimed method. See MPEP § 716.02(d).

Further, Note those unknown or **future known** cancers yet to be discovered, which must require to additional or future research to discover, establish or verify their treatments. Therefore, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

*Genentech*, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factor and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to

engage in *undue experimentation* to test instant combination to treat any cancers or tumors encompassed in the instant claims, with no assurance of success.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 101-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514, of record) in view of The Merck Index, (12th ED), 1996, and Miwa et al. European Journal of Cancer (1998), 34(8), 1274-1281

Vite et al. discloses that the instant particular compound (see Example 3 at page 48) is useful in treating various types of cancers or tumors including the cancers recited in the instant claims 105-110 (see page 8-10). More important, Vite et al. discloses that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment. See page 10.

The prior art does not expressly disclose the employment of the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

The Merck Index teaches that fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy, i.e., combing with other anti-cancer agents as cancer chemotherapy drug regimens (see MISC-10).

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer, since the instant particular compound is known to be useful in treating various types of cancers or tumors including the cancers herein and also useful in combination with known anti-cancer and cytotoxic agents for cancer treatment according to Vite et al.

Moreover, fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy according to The Merck Index. Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be finally converted to 5-fluorouracil (5-FU) by

dThdPase in tumors, and should be much safer and more effective than 5-FU, for treating cancers or various types of tumors according to Miwa et al.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine and the instant compound, both known useful for the same purpose, i.e., treating cancers, would improve the therapeutic effects for treating the same, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Further, the teachings of Vite et al. that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment, and the combination cancer chemotherapy drug regimens in Merck Index, have clearly provided the motivation for the combination claimed herein.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 101-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 12 of U.S. Patent No. 6,686,380.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent, i.e. claim 12, is drawn to the same cancer or tumor treatment method comprising administering the same compound as herein with a chemotherapeutic agent. In particular, the patent discloses that chemotherapeutic agents includes pyrimidine analogs (see col.11 line 66). 5-Fluorouracil and its prodrug capecitabine are known pyrimidine analogs (see Merck Index ,THER-13).

Thus, the instant claims 101-112 are seen to anticipate claim 12 of U.S. Patent No. 6,686,380.

Claims 101-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33-34 and 57-58 of U.S. Patent No. 6,605,599.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent, i.e. claims 33-34 and 57-58, are drawn to the same cancer or tumor treatment method comprising administering the same compound as herein with a chemotherapeutic agent. In particular, the patent discloses that chemotherapeutic agents includes pyrimidine analogs (see col.11 line 66). 5-Fluorouracil and its prodrug capecitabine are known pyrimidine analogs (see Merck Index ,THER-13).

Thus, the instant claims 101-112 are seen to anticipate claims 33-34 and 57-58 of U.S. Patent No. 6,605,599.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
November 13, 2004

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